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ORIGINAL ARTICLE

Synthesis of some new substituted iodoquinazoline derivatives and their antimicrobial screening

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6-Iodo-2-thienylquinazolin-4(3H)-one;
Antimicrobial screening

Abstract A new series of 6-iodo-2-thienylquinazolin-4(3H)-one and its fused heterocyclic analogs were prepared and screened for their antimicrobial activity. Compounds **4**, **8**, **14** and **24** showed remarkable broad spectrum antimicrobial activity. The fused heterocycles, 1,2,4-triazino[3,4-c]quinazoline, benzimidazo[1,2-c]quinazoline and quinazoline-bearing thiazolidinone moiety proved to contribute for antimicrobial activity. The detailed synthesis and their antimicrobial screening are reported.

1. Introduction

The spread of antibiotic resistance among pathogenic bacteria has become a major problem for the clinical management of infectious diseases (Ghebremedhin et al., 2009). Such medical health problems have encouraged many medicinal chemists to search for novel antibacterial agents other than the analogs of existing antibiotics (Dougherty and Friedberg, 2010; Bailey and Summers, 2008; Edwards and Biagini, 2006). Certain quinazoline derivatives showed a remarkable activity against the opportunistic infections of *Pneumocystis carinii* and *Toxoplasma gondii* (Gangjee et al., 2008; Cody et al., 2004). These microorganisms proved to be the clinical cause of death in patients with immune-compromised diseases such as acquired immune deficiency syndrome (AIDS). Recently, certain quinazoline derivatives are reported as an efficient chemosensitizer of antibiotic activity in *Enterobacter aerogenes*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* resistant strains (Chevalier et al., 2010). More recently, some alkylaminoquinazoline derivatives are reported to restore antibiotic activity in Gram-negative resistant isolates (Mahamoud et al., 2011).

Based on the aforementioned facts and as a continuation of our previous efforts aiming to locate new active quinazoline-based antimicrobial agents with enhanced potency, reduced toxicity and low cost, a new series of 6-iodoquinazoline derivatives were synthesized and screened (Aziza et al., 1996; Allimuny et al., 1996; Ghorab et al., 1995). In this work, the quinazoline

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analogs were designed to contain some functional groups that are believed to contribute to the antimicrobial activity such as $-NHCOCH_3$, $-SCH_2CONH_2$ in addition to a collection of fused or connected heterocycles to the quinazoline ring such as benzimidazole, 1,3-thiazolidine, 1,2,4-triazole. The new synthesized compounds were screened against Gram negative *Escherichia coli*, Gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*) and pathogenic fungi (*Saccharomyces cerevisiae, Candida albicans*).

2. Experimental

All melting points were recorded in open capillaries and were uncorrected. Microanalysis was conducted on a Heraeus instrument, results were within ±0.4% of the theoretical values, thin layer chromatography was performed on Merck 5 × 10 cm plates, pre-coated with silica gel GF_{254} using short wavelength UV light for visualization (EtOAc, hexane 2:1). All fine chemicals and reagents were purchased from Aldrich chemical Co., USA. ^{1}H NMR spectrum was recorded on a Varian Gemini 200 MHz spectrophotometer; chemical shifts were in σ (ppm) values downfield from tetramethylsilane as the internal standard. The following organisms were used in the antimicrobial screening. *E. coli* ATCC 10536, *S. aureus* ATCC 06538, *B. subtilis* ATCC 6633, *S. cerevisiae* ATCC 9763 and *C. albicans* ATCC 1023.

The starting materials 6-iodo-2-thienyl-1,3-benzoxazin-4(3H)-one (**1**), 6-iodo-2-thienylquinazolin-4(3H)-one, 3-amino-6-iodo-2-thienylquinazolin-4(3H)-one (**7**), 6-iodo-2-thienyl-3,4-dihydroquinazolin-4-one (**20**) and 6-iodo-2-thienyl-3,4-dihydroquinazolin-4-thione (**22**) were synthesized according to reported procedures.

*2.1. 2-Thienyl-6-iodo-3-(4-bromophenyl)-quinazoline-4(3H)-one (**2**) (Al-Obaid et al., 2009)*

A mixture of compound (**1**, 3.55 g, 0.01 mol) and 4-bromoaniline (2.5 g, 0.015 mol) in dry pyridine (15 ml) was heated under reflux for 24 h. The reaction mixture was cooled, treated with cold hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol Table 1. ^{1}H NMR (DMSO-d_6), 2: δ 7.26 (t, 1H, J = 4-Hz, thiophene-H), 7.70 (d, 1H, J = 0.5-Hz, thiophene), 7.86–7.88 (dd, 1H, J = 41.5, 8.5-Hz, quinazoline-H), 7.90 (d, 1H, J = 4.0-Hz, thiophene-H), 8.00–8.60 (m, 6H, Ar-H).

*2.2. 2-(2-Thienyl)-6-iodo-3-[-2-substituted phenyl]-3H-quinazoline-4-one (**3a**,**b**) (Abdel-Hamid, 2001)*

A mixture of 4H-3,1-benzoxazin-4-one derivative (**1**, 3.55 g, 0.01 mol) and the appropriate aromatic amine (0.015 mol) in dry pyridine (15 ml) was heated under reflux for 18 h. The solvent was removed under reduced pressure. The obtained solid was filtered, washed with diluted HCl and crystallized from an appropriate solvent Table 1. ^{1}H NMR (DMSO-d_6), **3a**: δ 5.00 (s, 2H, NH_2), 6.90–7.80 (m, 7H, Ar-H), 7.90 (d, 1H, J = 4.0 Hz, thiophene-H), 8.15 (d, 1H, J = 1.50-Hz, quinazoline-H), 8.34 (d, 1H, J = 8.5 Hz, quinazoline-H). Compound **3b**: δ 3.69 (s, 3H, OCH_3), 6.85–7.75 (m, 6H, Ar-H), 7.86–7.88 (dd, 1H, J = 1.5, J = 8.5 Hz, quinazoline-H), 7.92 (d, 1H, J = 4.0 Hz, thiophene-H), 8.15 (d, 1H, J = 1.5 Hz, quinazoline-H), 8.35 (d, 1H, J = 8.5 Hz, quinazoline-H).

*2.3. 6-(2-Thienyl)-2-iodo-benzimidazo[1,2-c]-quinazoline (**4**) (Abdel-Hamid, 1997)*

A mixture of compound (**1**, 3.55 g, 0.01 mol) and *o*-phenylenediamine (1.08, 0.01 mol) and fused sodium acetate in glacial acetic acid (15 ml) was heated under reflux for 24 h. The mixture was cooled and the obtained solid was filtered, washed with water, dried and crystallized from ethanol Table 1. ^{1}H NMR (DMSO-d_6), **4**: δ 7.26–7.83 (m, 7H, Ar-H), 7.91 (d, 1H, J = 4.0 Hz, thiophene-H), 8.15 (d, 1H, J = 1.50-Hz, quinazoline-H), 8.34 (d, 1H, J = 8.5 Hz, quinazoline-H).

*2.4. 2-(2-Thienyl carbonylamino)-5-iodo-N-[isobutyl]-benzamide (**5**) (Abdel-Hamid, 1999)*

A mixture of 4H-3,1-benzoxazin-4-one derivative (**1**, 3.55 g, 0.01 mol) and isobutyl amine (2.19 g, 0.003 mol) in dry pyridine (15 ml) was heated under reflux for 18 h. The solvent was removed under reduced pressure. The obtained solid was filtered, washed with diluted HCl and crystallized from glacial acetic acid Table 1. ^{1}H NMR (DMSO-d_6), **5**: δ 1.1 (d, 6H, J = 8 Hz $(CH_3)_2CH$–), 2.3 (m, 1H, $(CH_3)_2CH$–CH_2), 3.16 (d, 2H, J = 8.00 Hz, N–$CH_2CH(CH_3)_2$), 7.27 (t, 1H, J = 4.00-Hz, thiophene-H), 7.71 (d, 1H, J = 0.5 Hz, thiophene-H), 7.87–7.89 (dd, 1H, J = 1.5, J = 8.5 Hz, Ar-H), 7.92 (d, 1H, J = 4.0 Hz, thiophene-H), 8.16 (d, 1H, J = 1.5 Hz, Ar-H), 8.32 (d, 1H, J = 8.5 Hz, Ar-H), 9.3 (s, 1H, CONH–CH_2), 12.36 (s, 1H, (Ph–NH–CO).

*2.5. 2-(2-Thienyl)-6-iodo-3-methyl-quinazoline-4-one (**6**)*

A mixture of 4H-3,1-benzoxazin-4-one derivative (1, 3.55 g, 0.01 mol) and N-methyl-formamide (30 ml) was heated under reflux for 6 h., on cooling, the separated solid was filtered, washed with water and crystallized from glacial acetic acid Table 1. ^{1}H NMR (DMSO-d_6), **6**: δ 2.61 (s, 3H, N–CH_3), 7.23 (d, 1H, J = 4.00 Hz, thiophene-H), 7.73 (d, 1H, J = 0.5 Hz, thiophene-H), 7.86–7.88 (dd, 1H, J = 8.5, J = 1.50-Hz, quinazoline-H), 7.95 (d, 1H, J = 0.5 Hz, thiophene-H), 8.14 (d, 1H, J = 1.5 Hz, quinazoline-H), 8.34 (d, 1H, J = 8.5 Hz, quinazoline-H).

*2.6. 9-Iodo-5-(2-thieno)-3H-2-thioxo-1,2,4-triazolo-[2,3-c]quinazoline-4-one (**8**)*

An equimolar amount of 4H-3,1-benzoxazin-4-one derivative (1, 3.55 g, 0.01 mol) and thiosemicarbazide (0.9 g, 30 ml) was fused together at 190 °C in an oil bath for 1 h, on cooling, the solid mass was dissolved in boiling glacial acetic acid (50 ml) and filtered, the filtrate was concentrated up to (10 ml) in vacuo and cooled, the resulting solid filtered, washed with water and crystallized from glacial acetic acid to afford **8** Table 1. ^{1}H NMR (DMSO-d_6), **8**: δ 7.26 (t, 1H, J = 4.00 Hz, thiophene-H), 7.70 (d, 1H, J = 0.5 Hz, thiophene-H), 7.88–7.89 (dd, 1H, J = 8.5, J = 1.50 Hz, Ar-H), 7.91 (d, 1H, J = 4.0 Hz, thiophene-H), 8.14 (d, 1H, J = 1.5 Hz, Ar-H), 8.33 (d, 1H, J = 8.5 Hz, Ar-H), 12.41 (s, 1H, CH–N).

Table 1 The physicochemical properties of new synthesized compounds.

No.	Compound	Solvent of crystallization	Melting point	Yield (%)	Molecular formula
1	**2**	Ethanol	237–239	71	$C_{18}H_{10}BrIN_2OS$
2	**3a**	Dioxane	270–272	65	$C_{18}H_{12}IN_3OS$
3	**3b**	Acetic acid	175–177	73	$C_{19}H_{13}IN_2O_2S$
4	**4**	Ethanol	221–223	66	$C_{18}H_{10}IN_3S$
5	**5**	Acetic acid	141–143	76	$C_{16}H_{17}IN_2O_2S$
6	**6**	Acetic acid	± 300	74	$C_{13}H_9IN_2OS$
7	**8**	Acetic acid	± 300	64	$C_{13}H_7IN_4S_2$
8	**9**	Acetic acid	230–232	73	$C_{17}H_{10}IN_3OS_2$
9	**10**	Acetic acid	220–222	77	$C_{18}H_{11}IN_4OS$
10	**11**	Acetic acid	230–232	81	$C_{21}H_{14}IN_3OS$
11	**12**	Ethanol	± 300	75	$C_{19}H_{12}IN_5OS$
12	**13**	Ethanol	280–282	69	$C_{24}H_{17}IN_4OS_2$
13	**14**	Ethanol	210–212	43	$C_{19}H_{12}IN_3O_2S_3$
14	**15**	Ethanol	200–201	50	$C_{21}H_{14}IN_3O_2S$
15	**16**	Acetic acid	223–225	70	$C_{14}H_{10}IN_3O_2S$
16	**18**	Acetic acid	209–211	65	$C_{14}H_9ClIN_3O_2S$
17	**21**	Ethanol	85–87	77	$C_{16}H_{15}IN_2OS$
18	**22**	Ethanol	225–226	63	$C_{12}H_7IN_2S_2$
19	**23**	Dioxane	260–262	72	$C_{14}H_{12}IN_3OS_2$
20	**24**	Acetic acid	± 300	63	$C_{20}H_{15}IN_4OS$

*2.7. 2-(2-Thienyl)-3-arylideneamino-6-Iodo-3,4-dihydroquinazoline-4-ones (**9**–**11**)*

A mixture of 2-(2-thienyl)-3-amino-6-Iodo-3,4-dihydroquinazoline-6-one 7 (3.69 g, 0.01 mol) and the appropriate aldehyde (0.015 mol) in glacial acetic acid (50 ml) was heated under reflux for 24 h., on cooling, the separated solid was filtered, washed with water and crystallized from glacial acetic acid to give **9**–**11** Table 1. ^{1}H NMR (DMSO-d_6), **9**: δ 7.21–7.9 (m, 7H, thiophene-H and quinazoline-H), 8.15 (d, 1H, J = 1.5 Hz, quinazoline-H), 8.34 (d, 1H, J = 8.5 Hz, quinazoline-H), 9.23 (s, 1H, –CH═N). Compound **10**: δ 7.27–8.06 (m, 7H, thiophene-H, pyridine-H and quinazoline-H), δ 8.15 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.35 (d, 1H, J = 8.5 Hz, quinazoline-H), δ 8.71 (d, 1H, J = 6 Hz, pyridine-H), δ 9.21 (s, 1H, CH═N). Compound **11**: δ 5.73 (d, 1H, J = 5 Hz, olefinic-H), δ 6.53 (d, 1H, J = 5 Hz, olefinic-H), δ 7.27–7.78 (m, 7H, Ar-H and thiophene-H), δ 7.87–7.89 (dd, 1H, J = 8.5 Hz, 1.5 Hz, quinazoline-H), δ 7.93 (d, 1H, J = 4 Hz, thiophene-H), δ 8.15 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.35 (d, 1H, J = 4.0 Hz, quinazoline-H), δ 9.21 (s, 1H, –CH═N).

*2.8. 2-(6-Iodo-4-oxo-2-[thienyl] quinazolin-3-(4H)-ylamino)-2-(pyridin-2-yl)-acetonitrile (**12**)*

A mixture of compound (10, 0.01 mol) and potassium cyanide (0.01 mol in 5 ml H_2O) in glacial acetic acid (30 ml) was refluxed for 4 h, the reaction mixture was cooled and diluted with 20 ml cold water, the separated solid was filtered, washed with water and crystallized from ethanol to afford 12 Table 1. ^{1}H NMR (DMSO-d_6), 12: δ 4.1 (s, 1H, N–*NH*–CH(Pyridyl)–CN), δ 5.21 (s, 1H, NH–*CH*(Ph)–CN), δ 7.27–7.92 (m, 7H, pyridine-H, thiophene-H and quinazoline-H), δ 8.14 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.35 (d, 1H, J = 8.5 Hz, quinazoline-H), δ 8.72 (d, 1H, J = 6 Hz, pyridine-H).

*2.9. 3-[1-(2-Pyridinyl)-1-(phenylthiomethyl)amino]-2-(thienyl)-6-iodo-4-(3H)quinazoline (**13**)*

An equimolar amount of compound (**10**, **12**) (29 g, 0.01 mol) and thiophenol (0.55 g, 0.05 mol) was fused together in an oil bath at 200 °C for 1 h, on cooling the solid mass was dissolved in boiling ethanol (50 ml) and filtered. The filtrate was concentrated to half its volume, the separated solid was filtered and crystallized from ethanol to give **13** Table 1. ^{1}H NMR (DMSO-d_6), 13: δ 4.4 (s, 1H, NH–), δ 5.1 (s, 1H, CH–S), δ 7.18–8 (m, 12H, pyridine-H, thiophene-H and Ar-H), δ 8.15 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.35 (d, 1H, J = 8 Hz, quinazoline-H), δ 8.72 (d, 1H, J = 6 Hz, pyridine-H).

*2.10. 2-(2-Thienyl)-3-[2-(thienyl)-4-oxo-1,3-thiazolidin-3-yl]-6-iodo-3,4-dihydroquinazolin-4-one (**14**)*

A mixture of (**9**, 2.32 g, 0.005 mol) and thioglycolic acid (0.9 g, 0.01 mol) and anhydrous sodium chloride (1 g) in dry toluene (10 ml) was heated to reflux for 18 h. The reaction mixture was then filtered while hot. The clear filtrate was evaporated under reduced pressure and the obtained solid was crystallized from ethanol to afford **14** Table 1. ^{1}H NMR (DMSO-d_6): δ 3.72 (s, 2H, CO–CH_2–S), δ 6.15 (s, 1H, S–CH–), δ 7.1–7.96 (m, 7H, thiophene-H and quinazoline-H), δ 8.13 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.35 (d, 1H, J = 8 Hz, quinazoline-H).

*2.11. 2-(2-Thieno)-3-(cinnamoylamino)-6-iodo-4-oxo-3H-quinazoline (**15**)*

A mixture of 2-(2-thienyl)-6-iodo-3-amino-quinazolin-4-one (**7**, 1.85 g, 0.005 mol) and cinnamoyl chloride (0.83 g, 0.005 mol) in dry dimethyl formamide (25 ml) was heated under reflux for 1 h. The reaction mixture was cooled, poured into ice and stirred. The produced solid was filtered off washed with water, dried and crystallized from ethanol to afford **15** Table

Table 2 Antimicrobial screening results of the tested compounds at 1 mg/ml concentration.

No.	Compound no.	*E. coli*	*S. aureus*	*B. subitilis*	*S. cerevisia*	*C. albicans*
1	**1**	–	–	+	–	+
2	**2**	–	+	–	–	+
3	**3a**	–	++	++	++	+
4	**3b**	–	+	+	+	++
5	**4**	+++	++	++	+++	+++
6	**5**	–	+	–	+	–
7	**6**	+	–	–	+	–
8	**7**	+	+	+	–	+
9	**8**	++	++	+++	+++	+++
10	**9**	+++	–	++	–	+
11	**10**	–	+	–	–	+
12	**11**	+	++	+	++	+
13	**12**	+	–	–	+	–
14	**13**	++	–	++	+	+
15	**14**	++	+++	+++	++	++
16	**15**	++	++	–	++	–
17	**16**	+++	–	+	+	+++
18	**18**	+	+	–	++	–
19	**20**	+	++	++	–	–
20	**21**	+	–	+	–	–
21	**22**	+++	++	++	–	–
22	**23**	+	++	–	+	+
23	**24**	++	++	++	++	++
24	Ampicillin	+++	+++	+++	NT	NT
25	Streptomycin	+++	+++	+++	NT	NT
26	Nystatin	NT	NT	NT	++	++

(–) Inactive (inhibition zone < 10 mm), (+) moderate activity (inhibition zone 10–15 mm), (++) active (inhibition zone 15–20 mm), (+++) remarkable activity (inhibition zone > 20 mm), (NT) = not tested.

1. ^{1}H NMR (DMSO-d_6), **15**: δ 6.8–7.98 (m, 11H, Ar-H), δ 8.15 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.35 (d, 1H, J = 8.5 Hz, quinazoline-H), δ 10.1 (bs, 1H, NH–CO).

*2.12. 2-(2-Thieno)-3-(acetylamino) -6-iodo-4-oxo-3H-quinazoline (**16**)*

A mixture of 2-(2-thienyl)-6-iodo-3-amino-quinazolin-4-one (**7**, 1.85 g, 0.005 mol) and acetyl chloride (1 g, 0.02 mol) in dry dimethyl formamide (10 ml) was stirred at room temperature for 1 h. The reaction mixture was concentrated under *vacuo* and the resulting solid was crystallized from methanol to afford **16** Table 1. ^{1}H NMR (DMSO-d_6): δ 2.7 (s, 3H, –CH_3), δ 7.26 (t, 1H, J = 4 Hz, thiophene-H), δ 7.7 (d, 1H, J = 0.5 Hz, thiophene-H), δ 7.86–7.88 (dd, 1H, J = 1.5 Hz, J = 8.5 Hz, Ar-H), δ 7.92 (d, 1H, J = 4 Hz, thiophene-H), δ 8.15 (d, 1H, J = 1.5 Hz, Ar-H), δ 8.35 (d, 1H, J = 8 Hz, Ar-H), δ 11.2 (bs, 1H, N–NH–CO).

2.13. 2-(2-Thieno) -6-iodo-3-amino-3,4-dihydroquinazolin-4-one (7)

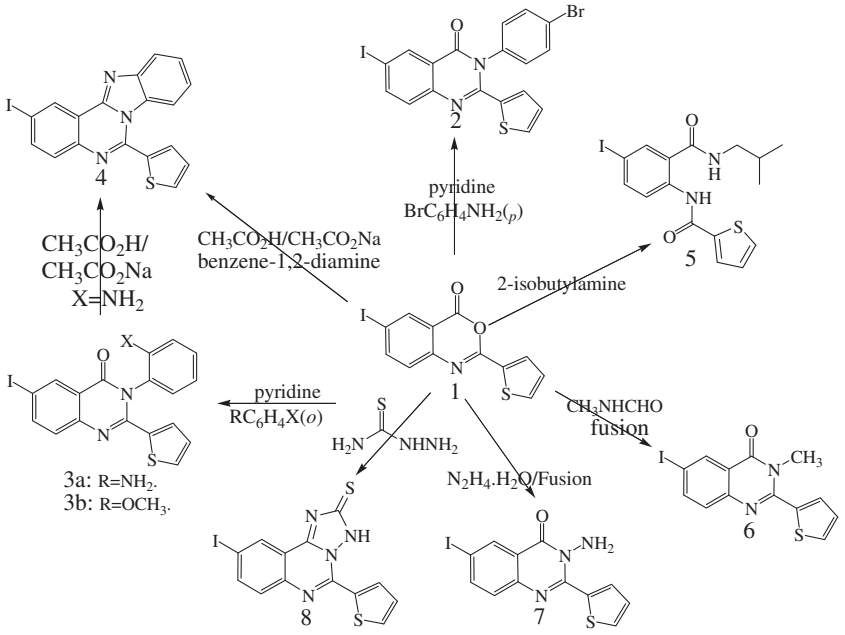
A mixture of compound (**16**, 2.05 g, 0.005 mol) and hydrazine hydrate (1 g, 0.01 mol) in *n*-butanol (10 ml) was heated under reflux for 18 h. The reaction mixture was concentrated, cooled and the separated solid was crystallized out from ethanol to afford **7** Table 1. ^{1}H NMR (DMSO-d_6): δ 5.6–5.7 (bs, 2H, NH_2), δ 7.27 (t, 1H, J = 4 Hz, thiophene-H), δ 7.73 (d, 1H, J = 0.5 Hz, thiophene-H), δ 7.85–7.87 (dd, 1H, J = 1.5 Hz, J = 8.5 Hz, quinazoline-H), δ 7.92 (d, 1H, J = 4 Hz, thiophene-H), δ 8.14 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.32 (d, 1H, J = 8.5 Hz, quinazoline-H).

*2.14. N-(6-Iodo-2-(2-thieno)-4(3H)-quinazolinon-3-yl)-2-chloroacetamide (**18**)*

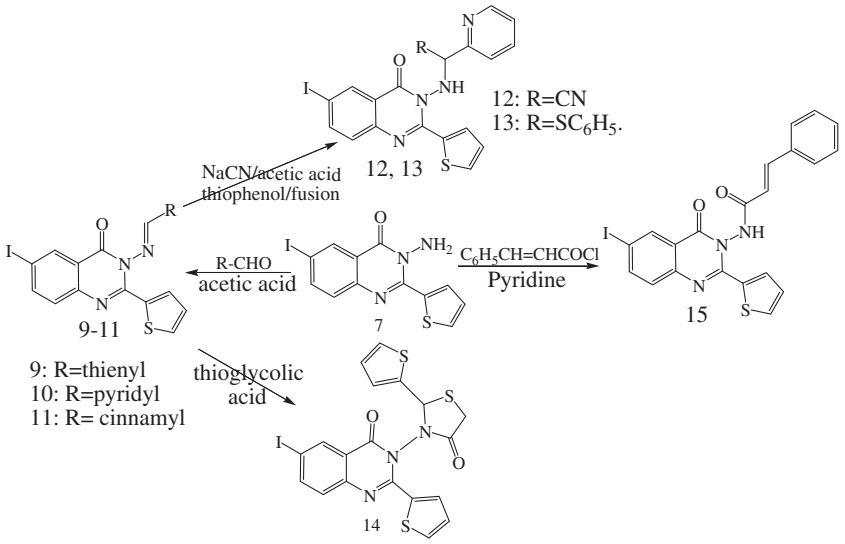
A mixture of compound (**7**, 1.85 g, 0.005 mol) and chloroacetyl chloride (0.85 g, 0.0075 mol) was heated under reflux in dry dimethyl formamide (15 ml) for 3 h. The reaction mixture was concentrated to half its volume, cooled, treated with ice-cold water (10 ml), the resulting solid was filtered, washed with water, dried and crystallized from ethanol to afford **18** Table 1. ^{1}H NMR (DMSO-d_6), 7: δ 4.23 (s, 2H, NH–CO–CH_2–Cl), δ 7.27 (t, 1H, J = 4 Hz, thiophene-H), δ 7.73 (d, 1H, J = 0.5 Hz, thiophene-H), δ 7.85–7.87 (dd, 1H, J = 1.5 Hz, J = 8.5 Hz, Ar-H), δ 7.92 (d, 1H, J = 4.0 Hz, thiophene-H), δ 8.15 (d, 1H, J = 1.5 Hz, Ar-H), δ 8.35 (d, 1H, J = 8.5 Hz, Ar-H), 9.12 (s, 1H, N–*NH*–CO–CH_2–Cl).

*2.15. 2-(2-Thienyl)-6-iodo-3, 4-dihydroquinazolin-4-one (**20**)*

A mixture of compound (**18**, 0.95 g, 0.002 mol) and anhydrous ammonium acetate (0.77 g, 0.01 mol) in glacial acetic acid (10 ml) was heated under reflux for 18 h. The reaction mixture was concentrated to half its volume, the separated solid was filtered, washed with water and crystallized from acetic acid to afford **20** Table 1. ^{1}H NMR (DMSO-d_6), **20**: δ 7.25 (t, 1H, J = 4 Hz, thiophene-H), δ 7.71 (d, 1H, J = 0.5 Hz, thiophene-H), δ 7.87–7.89 (dd, 1H, J = 1.5 Hz, J = 8.5 Hz, Ar-H), δ 7.91 (d, 1H, J = 4 Hz, thiophene-H), δ 8.15 (d, 1H,



Scheme 1



Scheme 2

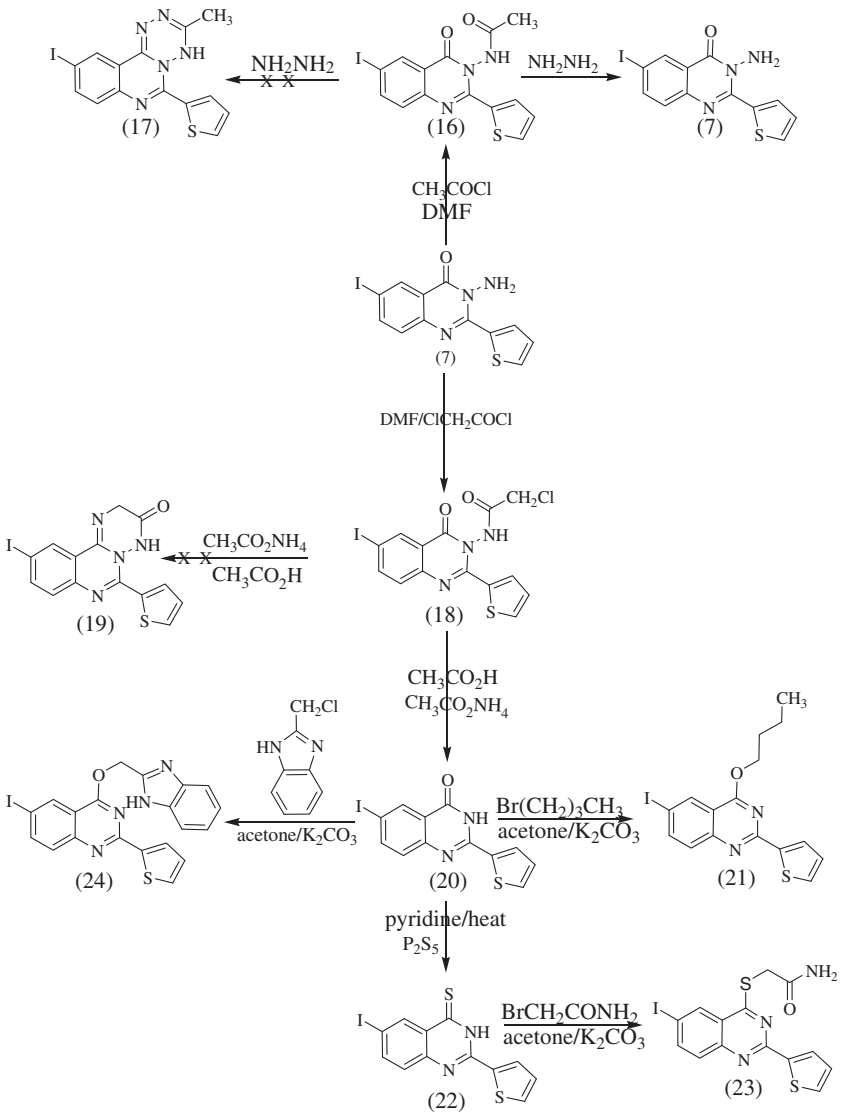
J = 1.5 Hz, Ar-H), δ 8.35 (d, 1H, J = 8.5 Hz, Ar-H), δ 12.6 (bs, H, –NH).

*2.16. 2-(2-Thieno)-4-n-butoxy-6-iodo-quinazoline (**21**)*

A mixture of compound (**20**, 1.77 g, 0.005 mol), *n*-butyl bromide (0.0075 mol) and anhydrous potassium carbonate (1 g) in dry acetone (25 ml) was heated under reflux for 8 h, the reaction mixture was then filtered while hot. The filtrate was evaporated under vacuum and the separated solid was washed with water and crystallized from ethanol to give **21** Table 1. ^{1}H NMR (DMSO-d_6), 21: δ 0.96 (t, 3H, J = 7.0 Hz, O–$CH_2CH_2CH_2CH_3$), δ 1.33–1.46 (m, 4H, J = 7.0 Hz, O–$CH_2CH_2CH_2CH_3$), δ 3.95–4.0 (t, 2H, J = 7.0 Hz, O–$CH_2CH_2CH_2CH_3$), δ 7.27 (t, 1H, J = 4.0 Hz, thiophene-H), δ 7.70 (d, 1H, J = 0.5 Hz, thiophene-H), δ 7.86–7.88 (dd, 1H, J = 1.5 Hz, J = 8.5 Hz, quinazoline-H), δ 7.91 (d, 1H, J = 4.0 Hz, thiophene-H), δ 8.14 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.34 (d, 1H, J = 8.5 Hz, quinazoline-H).

*2.17. 2-(2-Thienyl)-4-(2-benzimidazolylmethyloxy)-6-iodo-quinazoline (**24**)*

A mixture of compound (**20**, 1.77 g, 0.005 mol) anhydrous potassium carbonate (2 g) in dry acetone (30 ml), anhydrous potassium carbonate (2 g) was added followed by the addition of 2-chloromethyl benzimidazole (1 g, 0.006 mol). The reaction mixture was heated under reflux for 48 h. The solvent was re-



Scheme 3

moved in vacuo and the obtained solid was crystallized from ethanol to give **24** Table 1. ^{1}H NMR (DMSO-d_6), **24**: δ 4.6 (s, 2H, O–CH_2-hetero), δ 7.26–7.92 (m, 9H, Ar-H, benzimidazole-H, NH, thiophene-H, and quinazoline-H), δ 8.15 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.35 (d, 1H, J = 8.5 Hz, quinazoline-H).

*2.18. 2-(6-Iodo-2-(thien-2-yl)-6-quinazolin-4-ylthio)-acetamide (**23**)*

To a solution of compound (**22**, 1.85 g, 0.005 mol) in dry acetone (30 ml), anhydrous potassium carbonate (2 g) was added followed by the addition of 2-chloroacetamide (0.7 g, 0.0075 mol). The reaction mixture was heated under reflux for 20 h, filtered while hot and the filtrate was evaporated in vacuo to give the crude product which was crystallized from ethanol to afford **23** Table 1. ^{1}H NMR (DMSO-d_6), **23**: 4.62 (s, 2H, S–CH_2–CO), δ 7.24 (t, 1H, J = 4.0 Hz, thiophene-H), δ 7.70 (d, 1H, J = 0.5 Hz, thiophene-H), δ 7.86–7.88 (dd, 1H, J = 1.5 Hz, J = 8.5 Hz, quinazoline-H), δ 7.91 (d, 1H, J = 4 Hz, thiophene-H), δ 8.15 (d, 1H, J = 1.5 Hz, quinazoline-H), δ 8.34 (d, 1H, J = 8.5 Hz, quinazoline-H), δ 12.3 (bs, 2H, –NH_2).

3. Antimicrobial testing

Nutrient agar plates were seeded using 0.1 of overnight cultures. Cylindrical plugs were removed from the agar plates using a sterile cork borer and 100 μL of the tested compound (1 mg/ml DMSO) was added to the well in triplicates. A blank solvent was used as control. Plates inoculated with the tested bacteria were incubated at 37 °C, while those of the fungi were incubated at 30 °C. The results were taken after 24 h of incubation and were recorded as the average diameter of inhibition zone in mm.

4. Antimicrobial screening

All the new synthesized compounds were subjected to antimicrobial screening by *in vitro* cup-plate technique (Mahamoud et al., 2011) using ampicillin, streptomycin and nystatin as the positive controls. Compounds **4**, **9**, **16** and **22** showed

remarkable activity towards the gram negative bacteria *E. coli*. The Gram positive bacteria *S. aureus* and *B. subitilis* proved to be sensitive toward compounds **3a**, **4**, **8**, **14**, **20**, **22** and **24**.

Compounds **4**, **8**, **14** and **24** showed very good activity toward the tested fungal strains, *S. Cerevsiae* and *C. albicans*.

Compounds **4**, **8**, **14** and **24** proved to be the most active broad spectrum antimicrobial agents in this study Table 2. A close check of the structures of the active compounds revealed that the remarkable antimicrobial activity was confined to the compounds that possess either fused or connected heterocycles to a quinazoline skeleton e.g. 1,2,4-triazino (**8**), or benzimidazo (**4**) ring, also attachment of benzimidazole and 1,3-thiazolidinone to quinazoline nucleus increased remarkably the antimicrobial activity.

In conclusion the present study revealed that the heterocyclic system 1,2,4-triazino[3,4-c]quinazoline and benzimidazo[1,2-c]quinazoline, in addition to the quinazoline ring bearing either benzimidazole or 1,3-thiazolidinone moieties could be useful as a template for future development through modification or derivatization to design a more potent antimicrobial agent.

5. Results and discussion

The strategy to synthesize the target compounds **1–24**, is shown in Schemes 1–3. The starting material 2-thienyl-4-oxo-6iodo-benzoxazine (**1**) was allowed to react with a variety of substituted aromatic amines and isobutylamine to furnish compounds **2, 3a, 3b** and **5**, respectively. Fusion of the benzoxazine derivative with o-phenylenediamine at a high temperature gave the cyclized benzimidazo-[1,2-c]quinazoline. Boiling compound **2** with *n*-methyl formamide or hydrazine hydrate affords compounds **6** and **7**, respectively. Reaction of thiosemicarbazide with the benzoxazine (**1**) in the least amount of boiling glacial acetic acid afforded the triazolo derivative (**8**). The 3-amino derivative (**7**) was reacted with different heterocyclic aldehydes and or cinnamaldehyde in boiling glacial acetic acid to give compounds **9–11** respectively. Subjecting the compound (**10**) to the action of HCN in glacial acetic acid and/or thiophenol (by fusion) afforded the additional derivatives (**12, 13**). Compound (**9**) was reacted with mercapto acetic acid (in benzene to produce thiazolidene-4-one derivative (**14**). Reaction of cinnamaldehyde chloride with compound **7** afforded compound (**15**). The 3-amino derivative (**7b**) was reacted with acetyl chloride to give the acetyl derivative (**16**) which upon treatment with hydrazine hydrate in ethanol failed to form the fused heterocyclic analog (**17**) but gives instead the 3-amino derivative (**7**). The latter compound was boiled with phosphorus pentasulphide in pyridine to give the corresponding thioxo analog (**22**). Compound (**20**) was subjected to alkylation by 2-chloromethyl benzoimidazole to give compounds **21** and **24**, respectively. Compound (**21**) was reacted with bromoacetamide in acetone containing anhydrous potassium carbonate to afford the analog (**23**).

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